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INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32717A/AZG	FOR FURTHER ACTION <small>See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)</small>	
International application No. PCT/EP 03/11084	International filing date (day/month/year) 07.10.2003	Priority date (day/month/year) 08.10.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/502		
Applicant ACADEMISCH ZIEKENHUIS GRONINGEN et al.		

<p>1. This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the opinion II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application

Date of submission of the demand 23.04.2004	Date of completion of this report 16.12.2004
Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Kling, I Telephone No. +49 89 2399-8471



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 03/11084

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-16 as originally filed

Claims, Numbers

1-15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/11084

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
 - the entire international application,
 - claims Nos. 1-7
 - because:
 - the said international application, or the said claims Nos. 1-7 relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 - the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - no international search report has been established for the said claims Nos.
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
 - the written form has not been furnished or does not comply with the Standard.
 - the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-15
Inventive step (IS)	Yes: Claims	
	No: Claims	1-15
Industrial applicability (IA)	Yes: Claims	8-15
	No: Claims	1-7 (see item V below)

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/11084

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1 to 7 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claims 1 to 7 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

The documents cited in the International Search Report are numbered D1 to D11 in the order of their listing in said Search Report. Unless otherwise indicated, reference is made to the passages cited in said Search Report.:

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 15 is not new in the sense of Article 33(2) PCT.

The document D1 = XP001135111 (R.M.Mesters) reported increased angiogenesis in the bone marrow of patients with acute myeloid leukemia (AML)
In conclusion thalidomide seems to have anti-angiogenic as well as anti-leukemic activity

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/11084

in AML.

The VEGF/VEGFR-2 pathway seems to play an important role in AML

They could recently induce a stable remission in a patient with second relapse of her AML refractory towards chemotherapy by administration of SU5416 (compassionate use) a tyrosine kinase inhibitor of VEGFR-2 and c-kit.

The immunomodulatory drug thalidomide inhibits angiogenesis in animal models.

Moreover, it has significant activity in refractory multiple myeloma. In a current phase II study for patients with primary refractory or relapsed multiple myeloma using a combination of thalidomide with hyper fractionated cyclophosphamide and dexamethasone (Hyper-CDT), we observed a partial remission in 12 of 14 evaluable patients (86%).

This teaching anticipates the subject-matter of claims 1 to 15.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 15 does not involve an inventive step in the sense of Article 33(3) PCT.

D2 = WO-A-98 35958 discloses the compounds of formula I which are used in the compositions and the methods of the present application, these compounds having angiogenesis inhibiting activity and inhibits the activity of the VEGF receptor tyrosine kinase and the growth of tumours.

The studies disclosed in D3 = XP-008002456 indicate that compounds that inhibit the effects of VEGF, such as PTK787/ZK 222584, have the potential to provide a novel, effective and well-tolerated therapy for the treatment of solid tumours.

The knowledge of D2 combined with the teaching of D3 would lead the skilled man to the subject-matter of claims 1 to 15 of the present application.

D4 = XP000971163 relates to PTK787/ZK 222584, a novel and potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, impairs vascular endothelial growth factor induced responses and tumour growth after oral administration

It remains to be explored whether chronic therapy as a single agent or cyclic therapy in

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/11084

combination with conventional antitumour therapies will be the best approach for the treatment of cancer.

D5 = XP001135110 discloses that the VEGF receptor tyrosine kinase inhibitor PTK787 inhibits proliferation and migration of multiple myeloma cells, and reduces paracrine-mediated responses to the bone marrow microenvironment. The studies have shown that multiple myeloma (MM) cell lines and patient cells express the high affinity VEGF receptor (VEGFR), fms-like tyrosine kinase (Flt-1), but not fetal liver kinase (Flk-1). Moreover, these studies have also begun to delineate the signaling cascades triggered by VEGF that induce proliferation and migration of MM cells. In this study, we examined the activity PTK787/ZK222584 (developed jointly by Novartis and Schering AG) a molecule designed to bind specifically to the tyrosine kinase domain of the VEGFR and inhibit angiogenesis. We show that PTK787/ZK222584 acts both directly on MM cells and in the bone marrow microenvironment. Specifically, PTK787/ZK222584 (1 to 5 μ M) inhibits proliferation of MM cells by 50%, as assayed by 3 H-thymidine (3 H-dT) uptake. The demonstrated anti-MM activity of PTK787/ZK222584, coupled with its anti-angiogenic effects, provide the framework for clinical trials of this agent to overcome drug resistance and improve outcome in MM.

In D6 = XP-009012042 Traxler et Al., the anilino-phthalazine derivative PTK787/ZK222584 (Phase I, co-developed by Schering AG, Berlin) is a potent and selective inhibitor of both the KDR and Flt-1 kinases with interesting anti-angiogenic and pharmacokinetic properties (orally bioavailable).

D7 = WO-A-02/41882 relates to a combination which comprises a first active ingredient which is a vasculostatic compound and a second active ingredient which decreases the activity of the epidermal growth factor (EGF), in particular, for the delay of progression or treatment of a disease associated with deregulated angiogenesis, especially a proliferative disease.

The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the documents D8 to D11 cited in the international search report could become relevant to assess whether claims 1 to 15 satisfy the criteria set forth in Article 33(1) PCT.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/11084

The Priority of the present application has to be checked to see whether the following documents are relevant or not:

D8 = WO03035047 combination therapy for treating patients suffering from pre-malignant colon lesions (e.g. polyps) and colon cancer, as well as other malignancies, is disclosed. The patient is treated concurrently with a cyclooxygenase-2 inhibitor and at least one compound selected from the group consisting of a microtubule interfering agent, an epithelial growth factor receptor tyrosine protein kinase inhibitor and a vascular endothelial growth factor receptor tyrosine kinase inhibitor.

D9 = WO03022282 discloses that patients suffering from renal carcinoma are treated with a 4-pyridylmethyl-phthalazine anti-angiogenesis agents. Patients having different tumour types, e.g. renal cancer, are treated with a 4-pyridylmethyl-phthalazine anti-angiogenesis agent while undergoing chemotherapy.

D10 = WO03059354 relates generally to the use of certain substituted fused or unfused pyridazine or pyridine derivatives which are KDR inhibitors in combination with other chemotherapeutic agents for use in treatment of diseases associated with abnormal angiogenesis and/or hyperpermeability and/or hyperproliferative diseases, such as cancer. Under cancer also leukemia.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

D11 = XP001135110 discloses that:

The VEGF receptor tyrosine kinase inhibitor PTK787 inhibits proliferation and migration of multiple myeloma cells, and reduces paracrine-mediated responses to the bone marrow microenvironment